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| 10/594,427      | 07/17/2008  | Masashi Isozaki      | 1029650-000178      | 2940             |

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BUCHANAN, INGERSOLL & ROONEY PC  
POST OFFICE BOX 1404  
ALEXANDRIA, VA 22313-1404

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| EXAMINER |
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SCHULTZ, JAMES

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| ART UNIT | PAPER NUMBER |
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1633

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| NOTIFICATION DATE | DELIVERY MODE |
|-------------------|---------------|

09/23/2011

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com  
offserv@bipc.com

|                              |                         |                     |  |
|------------------------------|-------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b>  | <b>Applicant(s)</b> |  |
|                              | 10/594,427              | ISOZAKI ET AL.      |  |
|                              | <b>Examiner</b>         | <b>Art Unit</b>     |  |
|                              | James D. (Doug) Schultz | 1633                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 May 2011.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 5) ☒ Claim(s) 1-12 and 14-18 is/are pending in the application.
- 5a) Of the above claim(s) 7 and 18 is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 1-6, 8-12, 14-17 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-302)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____.                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____.  | 6) <input type="checkbox"/> Other: ____.                          |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 25, 2011 has been entered and considered. Rejections and/or objections not reiterated from the previous office action mailed May 25, 2011 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments with respect to the rejoinder of claims 8 and 9 are adopted, and the restriction against these claims is thus withdrawn. Claim 13 has been cancelled. Claims 7 and 18 are drawn to a phospholipid other than the elected phospholipid and a non-elected method, respectively, and both remain withdrawn.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8-12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), in view of Mayer et al. (U. S. Patent Number 5,616,341). This rejection is repeated for the same reasons of record as set forth in the action mailed April 19, 2010, and is reproduced below with responses to applicants traverse following.

The claims of the instant invention are drawn to a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, and an interior aqueous phase in the vesicle at a pH of up to 5, wherein the liposome has a drug loaded therein, and wherein the vesicle is modified with a hydrophilic macromolecule only on its exterior surface, and the hydrophilic macromolecule is introduced as a phospholipid derivative of the hydrophilic macromolecule, or the liposome preparation according to claim 1, wherein the drug is one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.05 mole / mole lipid, or wherein the drug loaded is at a concentration of 0.1 mole / mole lipid, or wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, or wherein the phospholipid is a hydrogenated phospholipid.

The invention also comprises the liposome preparation according to claim 1 wherein the lipid bilayer further comprises a cholesterol moiety, or a lipid other than the primary lipid component, or a basic compound containing a group selected from amino group, amidino group, and guanidino group as its component, or wherein the basic compound is 3,5-dipentadecyloxybenzamidinium hydrochloride, or wherein the hydrophilic macromolecule is

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polyethylene glycol having a molecular weight of 500 to 10,000 Dalton, or wherein the , or wherein the liposome preparation has an average size of 40 to 140 nm, or 50 to 130 nm, or 60 to 120 nm. The invention also comprises the liposome preparation according to claim 1, wherein the interior aqueous phase has a pH of 2 to 5.

Haragai et al teach a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, wherein the liposome has rhodamine loaded therein, and wherein the vesicle is modified with a hydrophilic macromolecule only on its exterior surface which is PEG, wherein the compound comprises 3,5, 3,5-dipentadecyloxybenzamidinium hydrochloride, and wherein the drug loaded is at a concentration of 0.02 mole / mole lipid, wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, and wherein the phospholipid is a hydrogenated phospholipid. Haragai also teaches liposome preparations having an average size of 100 nm. The liposomes of Haragai also have PEG only on the exterior (see pg. 1285, rt column first paragraph). Haragai also suggest that the preferential and selective binding characters of PEG-coated TRX-20 liposomes are useful tools for development of drug targeting system.

Haragai does not teach the liposomes having an interior aqueous phase in the vesicle at a pH of up to 5, or wherein the drug is the one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.1 or .5 mole / mole lipid.

Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5.

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Neither Mayer nor Haragai et al teach the drug loaded at a concentration of 0.1 mole / mole lipid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate phosphatidylcholine into the liposomes of Haragai et al. since phosphatidylscholine is a well known phospholipid commonly used in the formulation of liposomes, as evidenced by its use in the liposomes of Mayer et al. The use of phosphatidylcholine is considered to be an art recognized equivalent and its use is considered to be one that would be reached in the process of routine optimization. Furthermore it would have been obvious to use such phosphatidyl containing low pH liposomes in the delivery of doxorubicin, since doxorubicin is a well-known anticancer treatment, the liposomal delivery of which (at a low pH) is evidenced by Mayer et al. Haragai et al. also teach that their liposomes are effective drug delivery vehicles for many types of molecules. Finally, it would have been obvious to one of ordinary skill in the art to load the doxorubicin of Mayer et al at 0.1 or 0.5 mole/mole, since these amounts are within the range of amounts that would be reached upon the practice of routine optimization.

#### Response to Request for reconsideration

Applicants traverse the rejection by arguing that neither Mayer nor Harigai suggested a liposome preparation comprising all the features of claim 1. In response, it is pointed out that this is not considered relevant, since as stated in the final rejection mailed November 5, 2010, it has not been alleged that either teach the instant invention independently; rather it is the combination that is considered to render the rejected invention obvious.

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Applicants argue that neither Mayer nor Harigai suggested that the problem of liposome stability for drugs which must be maintained at low pH could be solved by including a hydrophilic macromolecule only on the exterior liposome surface of a unilamellar vesicle. Applicants also assert that Mayer proposed a distinctly different approach to providing for long term storage, and point to col. 16-17 of Mayer for reference. In response to the latter point, it is noted that column 16 is the last column of Mayer (i.e. there is no column 17), and column 16 consists only of claims which have nothing to do with storage. Regarding both points, there is no requirement that Mayer or Harigai appreciate, understand, or otherwise disclose these alleged benefits if the curative resulting product exists in or is suggested by the prior art, which is considered to be true instantly. It is well established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See M.P.E.P. 2112. Furthermore, the arguments directed to improved storage and stability are features that are not recited in the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., improved storage and stability) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

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improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 10-12, and 14-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,676,971, in view of Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), and Mayer et al. (U. S. Patent Number 5,616,341). This rejection is repeated for the same



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reasons of record as set forth in the action mailed April 19, 2010, and is reproduced below with responses to applicants traverse following.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to pegylated liposomes, which embrace the scope of the instant claims drawn to pegylated liposomes that have a pH up to 5, and contain doxorubicin. Although the patented claims do not teach liposomes that have a pH up to 5, and contain doxorubicin, this feature is disclosed above in the combinations of Haragai and Mayer et al. as described above. Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5. Haragai et al. teach the use of 3,5 pentadecyloxybenzamide containing liposomes as taught above.

It would have been obvious to use 3,5 pentadecyloxybenzamide-containing liposomes as taught by Haragai et al. with low pH interiors in the delivery of doxorubicin as taught by Mayer et al., since doxorubicin is a well-known anticancer treatment, the low pH liposomal delivery of which is also well known, as evidenced by Mayer et al.

#### Response to Request for reconsideration

Applicants' response does not address this rejection. Applicants' are reminded of the requirement under 37 CFR 1.111(b) to reply to each rejection or objection set forth in the prior Office action. The reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references.

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Failure to do so will result in a Notice of Non-Compliance. In the absence of any response, the present rejection is maintained.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. (Doug) Schultz whose telephone number is (571)272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D. (Doug) Schultz/  
Primary Examiner, Art Unit 1633